

## No association of common *VCP* variants with sporadic frontotemporal dementia.

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## **Abstract**

Mutations in the gene for valosin containing protein (*VCP*) cause autosomal dominant inclusion body myopathy associated with Paget disease and frontotemporal dementia (IBMPFD). To investigate the role of this novel gene in sporadic forms of frontotemporal dementia (FTD), we genotyped 27 single nucleotide polymorphisms covering the entire *VCP* genomic region in 198 patients with sporadic FTD and 184 matched controls from Germany. No significant association could be demonstrated. There is no evidence, that common variants in *VCP* confer a strong risk to the development of sporadic FTD.

**Introduction.** Recently, seven missense mutations in the valosin containing protein gene (*VCP*; OMIM #601023) on chromosome 9p13-p12 have been identified to cause a rare autosomal dominant multisystem disorder with frontotemporal dementia (FTD), called inclusion body myopathy associated with Paget disease of bone and frontotemporal dementia (IBMPFD; OMIM #167320). *VCP* is a ubiquitous member of the AAA-ATPase superfamily and has been associated with several essential cell protein pathways [15], such as cell cycle, nuclear envelope construction, postmitotic Golgi reassembly, homotypic membrane fusion, DNA damage response and suppression of apoptosis [5, 9-12]. Furthermore, *VCP* plays a role in the ubiquitin-proteasome dependent degradation of cytosolic proteins. Mutations in *VCP* can lead to the accumulation of ubiquitinated proteins within cells and to the alteration of the ubiquitin-proteasome system [3, 17]. The *VCP* protein also binds to expanded polyglutamine (poly-Q) protein aggregates and participates in poly-Q induced neuronal degeneration [6, 7]. The *VCP* gene consists of 17 exons, spans a genomic region of 16 kb and the mutations described so far are clustered in a region around Exon 3 (R93C; R95G), Exon 5 (R155H/P/C; R159H; R191Q) and Exon 6 (A232E), which encodes the N-terminal CDC48 domain, a flexible linker domain and the first AAA-ATPase domain [4, 13, 16].

FTD may represent, like many other neurodegenerative diseases, a genetically complex disorder where in addition to susceptibility genes that confer risk to the sporadic forms of the disease, mutations in specific genes are essential for disease development. Mutations are known for genes such as the microtubule-associated protein tau (*MAPT*, OMIM #157140; [8]), presenilin 1 (*PSEN1*, OMIM #104311; [1]) and the endosomal ESCRTIII-complex subunit (*CHMP2B*, OMIM #609512; [14]), all of which cause an autosomal dominant familial form. Common variants of genes causing familial forms of neurodegenerative diseases have been repeatedly shown to be also associated with sporadic forms. Since the known familial *VCP* mutations cause IBMPFD [2-4, 16], it is reasonable to investigate also the relationship of *VCP* in patients with sporadic FTD. In this study, we genotyped 27

single nucleotide polymorphisms (SNPs) covering the complete chromosomal region of the *VCP* gene, including the neighbouring genes *C15orf131*, *FANCG* and *PIGO* as well as the non-translated small cytoplasmic RNA (scRNA) *SRP\_RNA-related*, determined the linkage disequilibrium (LD) structure and explored single marker and haplotype associations with sporadic FTD.

**Results.** A region showing high  $D'$  values was identified at the *VCP* 5' UTR/promoter region and the whole *FANCG* gene (between rs2299612 and rs584040), and additionally within *VCP* spanning from Intron 2 (rs10972300) to Intron 6 (rs622945). Within the *VCP*-region there appear to be two areas, one in the first Intron of *VCP*, and the second between Exon 17 and the 3'UTR region, that show considerable low pairwise  $D'$  and  $r^2$  values, indicating a region were fractionation by recombinational events occurred (Supplementary Fig. 1). In addition, most pair-wise  $r^2$  values are low among the markers within the *VCP*-region. Only a very few small patches of considerable high  $r^2$  values could be identified.

No significant association for any single markers was found in this sample (See Supplementary material Table 1). Additionally, we observed no significant association for the haplotype (Block 2, see Supplementary material Fig. 1 and Table 2), which covers the genomic region, of *VCP* Exon 3 and Exon 6 where the mutations have been described in patients with IBMPPFD. In addition, the seven patients with FTD and ALS also did not show any obvious differences regarding their genotype distributions compared to all other patients with FTD. The p-values for markers (rs637885 and rs622945) in *VCP* Intron 5 and 6 represents uncorrected values and are clearly not significant when applying a correction for multiple testing which is required due to the multiple comparisons performed in this region (data not shown). Similarly, the same considerations apply for the markers (rs7048389 and rs642296) at the *VCP* 3' UTR region covering a putative non-translated scRNA and

three SNPs within the *FANCG* gene (rs587118, rs504082 and rs584040). Only clearly non-significant p-values were found for the *C9orf131* gene, located 3' of *VCP* and for the 5' *PIGO* gene region.

**Discussion.** Using a carefully ascertained case-control sample from two specialized dementia outpatient units with a research focus on FTD we performed a whole gene approach by genotyping of 27 densely spaced SNPs, which covered the entire genomic region of *VCP* including the promoter and neighboring genes and determined the LD structure. Single marker as well as haplotype analysis did not reveal evidence of a significant association of common *VCP* variants with sporadic forms of FTD or any remarkable differences in patients with ALS/FTD. Although not being significant the trend observed at the *VCP* introns 5 and 6 may reflect a rare contribution of *VCP* in sporadic FTD. It is likely, that the known *VCP* mutations in IBMPFD, cause distinct pathologies compared to sporadic FTD and familial FTD with ubiquitin-positive intracytoplasmic inclusions (FTLD-U) without *VCP* mutations. Such phenotypes are characterized by ubiquitin-positive neuronal intranuclear inclusions, dystrophic neuritis and in some cases ubiquitin-negative neuronal aggregates [2, 3]. For the development of sporadic FTD we also can rule out any involvement of *C15orf131*, an uncharacterized transcript, with predominant expression in the brains of adults, located 3' of *VCP*. The same non-significant trend could be observed for the 5' genes *FANCG*, and *PIGO* (for details see Supplementary material).

In summary, this study does not provide strong evidence that common genetic variations of *VCP* are associated with an increased risk to develop FTD. Our genetic findings, however, do not rule out a possible functional involvement of *VCP* in the pathogenesis of neurodegeneration in FTD.

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## **Supplementary material**

### **Methods**

Patients with FTD (N=198) were recruited at the memory outpatient units with a special focus on FTD at the TU-Munich and the University of Regensburg and thoroughly diagnosed according to current diagnostic criteria [6]. The patient sample had a male to female ratio of 1.2, showed an age at onset of  $63.1 \pm 10.3$  years (mean  $\pm$  SD) and consisted of individuals with the diagnosis of FTD (N=147), FTD/ALS (FTD with amyotrophic lateral sclerosis, N=7), PPA (primary progressive aphasia, N=16), and SD (semantic dementia, N=24). The control group (N=184) was matched for age, geographical location and ethnicity and consisted of cognitively healthy elderly subjects ( $62.9 \pm 11.8$  years) who were recruited from the memory clinic and community based geriatric day-care units. The cognitive status of individuals in the control group was assessed using the Mini Mental State Examination (MMSE; [3]) and individuals who scored under 28 were excluded. Blood samples of each subject were taken after informed consent had been obtained. The study protocol was approved by the institutional review boards of both universities.

Information for all 27 SNPs were derived from public databases, the average intermarker distance of all SNPs was 1.9 kb. Genotyping was performed through a PCR based primer extension reaction and detection of the allele-specific extension products by matrix-associated laser desorption/ionization time of flight (MALDI-TOF) mass spectrometry (Sequenom, San Diego, CA) at the Dept. of Psychiatry, Munich. The average call rate for all SNPs was above 94% and the genotype distributions of all SNPs were in Hardy-Weinberg equilibrium. LD was estimated by  $D'$  and  $r^2$  as implemented in Haploview [1]. Allelic/genotypic associations with FTD were tested by logistic regression analyses using age and sex as covariates. Haplotypic associations were calculated using  $\chi^2$  tests as implemented in Haploview. Corrections for multiple testing were considered if mandatory.

**Additional information:**

FTD like many other diseases may represent a genetically complex disease where genetic risk factors in addition to the autosomal dominant forms, due to mutations in the *MAPT* [4], the endosomal ESCRTIII-complex subunit *CHMP2B* [7] or *PSEN1* genes [2], may confer risk to the disease. However, the identification of genetic risk factors in patients with FTD struggles behind the genetic research in other neurodegenerative diseases, such as Alzheimer's and Parkinson's disease. Recent findings that genetic variations within genes usually associated with monogenic forms of neurodegenerative diseases, such as  $\alpha$ -synuclein in Parkinson [5] and the Tau haplotype in FTD [8] may also confer risk to the sporadic forms led us to examine the role of common *VCP* variants in sporadic forms of FTD.

*FANCG* is a gene which is involved in Fanconi anemia, an autosomal recessive disorder with diverse clinical symptoms, including developmental anomalies, bone marrow failure, and early occurrence of malignancies. The *PIGO* gene encodes a protein that is involved in glycosylphosphatidylinositol (GPI)-anchor biosynthesis found on many blood cells and serves to anchor proteins to the cell surface.

Due to the relatively small sample size it might be speculated that we missed a possible association due to lack of statistical power. However, a one-sided power analysis revealed that, at a significance level of  $\alpha=0.05$ , we had a power of 88% (two-sided: 80%) to detect a risk allele of 20% frequency, which mediates a relative risk of 2.0. Thus, based on our sample size we had a reasonable statistical power to identify genetic effects conferring a two-fold or higher risk.

**Table 1: SNP description, allele distribution and association with FTD**

SNP	Position (hg17)	Gene(s)	Role	Alleles	Major allele frequencies (Cases/Controls)	p-values*
rs10491510	35030245	C15orf131	Promoter	C/T	0.989 / 0.980	0.257
rs615474	35033291	C15orf131	Coding exon 3	G/T	0.045 / 0.044	0.952
rs2298312	35034493	C15orf131	Coding exon 3	A/T	0.051 / 0.032	0.327
rs813422	35036291	C15orf131	3' UTR	T/G	0.252 / 0.211	0.253
rs525106	35039468	SRP_RNA	scRNA	C/T	0.555 / 0.515	0.421
rs7048389	35039508	SRP_RNA	scRNA	T/C	0.055 / 0.024	0.054
rs10972298	35040840	VCP	3' UTR	G/A	0.956 / 0.929	0.46
rs642296	35041269	VCP	3' UTR	T/C	0.467 / 0.421	0.077
rs511228	35043336	VCP	3' UTR	G/A	0.261 / 0.214	0.411
rs684562	35050302	VCP	Intron 13 (boundary)	T/C	0.300 / 0.240	0.145
rs12004343	35050688	VCP	Intron 12 (boundary)	T/A	0.012 / 0.006	0.937
rs2258240	35050955	VCP	Intron 11 (boundary)	T/C	0.246 / 0.216	0.391
rs607671	35052613	VCP	Intron 7	A/G	0.254 / 0.239	0.389
rs514492	35052972	VCP	Intron 7 (boundary)	C/T	0.213 / 0.182	0.227
rs622945	35053724	VCP	Intron 6	A/G	0.309 / 0.263	0.089
rs623318	35053789	VCP	Intron 6	T/G	0.758 / 0.737	0.297
rs637885	35054788	VCP	Intron 5	A/G	0.315 / 0.259	0.081
rs10972300	35058201	VCP	Intron 2 (boundary)	T/C	0.197 / 0.173	0.214

rs2073575	35058640	VCP	Intron 1	A/T	0.056 / 0.035	0.236
rs2299612	35060726	VCP	Intron 1	C/T	0.785 / 0.785	1.0
rs2299613	35061091	FANCG	3' UTR	C/T	0.207 / 0.206	0.558
rs739844	35062001	FANCG	3' UTR	C/G	0.215 / 0.190	0.881
rs587118	35064917	FANCG	Intron 12 (boundary)	T/C	0.506 / 0.468	0.062
rs554098	35067441	FANCG	Intron 4 (boundary)	T/C	0.226 / 0.194	0.47
rs504082	35069361	FANCG	Intron 1 (boundary)	G/T	0.313 / 0.260	0.067
rs584040	35070830	FANCG	Promoter	T/C	0.257 / 0.198	0.057
rs505297	35080782	PIGO	Intron 7	A/C	0.246 / 0.214	0.164

**Table 2: Common haplotypes, frequencies and associations with FTD**

<b>Block</b>	<b>Sequence</b>	<b>Frequency (Cases/Controls)</b>	<b>p value</b>
<b>Block 1</b>			
1.1	CG	0.743 / 0.761	0.573
1.2	TA	0.248 / 0.218	0.342
1.3	CA	0.009 / 0.021	0.188
<b>Block 2</b>			
2.1	CTCGGTGGGAG	0.242 / 0.259	0.596
2.2	CGCGGTGGGAG	0.232 / 0.262	0.367
2.3	CTCAACGAGAG	0.186 / 0.173	0.649
2.4	TTTGGTCAACA	0.151 / 0.151	0.990
2.5	TTTGGTGAACA	0.076 / 0.052	0.204
2.6	TTTGGTCAGCG	0.054 / 0.030	0.114
2.7	TTTGGTGAGCG	0.012 / 0.019	0.492
2.8	CTCGACGAGAG	0.003 / 0.021	0.031



**Legends to the Tables and Figure:****Table 1:**

The locations of the SNPs on Chromosome 9 and *VCP*, *C15orf131* (*MGC41945*), *FANGC*, *PIGO* and the scRNA (SRP\_RNA related) according to the UCSC map (hg17) are demonstrated. The distribution of the alleles in cases and controls and the association result of a regression analysis with p-values are shown. \* = uncorrected.

**Table 2:**

All haplotypes with a frequency > 1% within the two LD blocks of the *VCP* gene (27 SNPs) in the German sample were tested for association with FTD using  $\chi^2$  statistics.

**Figure 1:**

Linkage disequilibrium structure of the *VCP* gene region. Pair-wise  $r^2$  values are intensity-coded: black = high  $r^2$  values, white = low  $r^2$  values. The two haplotype blocks indicated by high  $D'$  values are superimposed. The genomic region is shown on top.

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